IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Helmut Meissner *et al.* Examiner: Evelyn Mei Huang

Serial No.: 09/965,766 Group Art Unit: 1625

Filed: September 28, 2001 Docket: 1/1150

For: ANTICHOLINERGICS, PROCESSES FOR PREPARING THEM, AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MICHAEL PAUL PIEPER UNDER 37 C.F.R. § 1.132

Sir:

I, Michael Paul Pieper, declare that:

1. I have studied Veterinary medicine at the University (School of Veterinary Medicine Hannover) Hannover, Germany from 1986 to 1991 (Degree: board certified veterinarian).

2. I did my doctoral thesis in Pharmacology from 1992 to 1994 and received a Ph.D. (Dr. med. vet.) from the School of Veterinary Medicine Hannover, Hannover, Germany in 1994.

3. Since 1994, I have been employed by Boehringer Ingelheim, presently in the Department of Pulmonary Research of Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

4. I am familiar with the above-identified patent application (hereinafter "the Meissner *et al.* application").

5. I am familiar with the U.S.P.T.O. Office Action dated May 13, 2003 and the prior art references cited therein: Banholzer I (U.S. Patent No. 5,770,738) and Banholzer II (U.S. Patent No. 5,654,314).

6. Under my responsibility and control, tropenol 3,3'-difluorbenzilic acid ester-methobromide (Example 34 of the Meissner *et al.* application) and scopine 3,3'-difluorbenzilic acid ester-methobromide (Example 35 of the Meissner *et al.* application) were tested according to the experimental procedure described in ANNEX 1 (Kallos-Pagel model).

7. The experiment according to ANNEX 1 determined that the bronchoprotective efficacy of tropenol 3,3'-difluorbenzilic acid ester-methobromide (Example 34 of the Meissner *et al.* application) and of scopine 3,3'-difluorbenzilic acid ester-methobromide (Example 35 of the Meissner *et al.* application) decreases after about 24 hours to a value of about 20% and 40% respectively. The graphic illustration of these results is depicted in ANNEX 2.

8. The experiment according to ANNEX 1 determined that the bronchoprotective efficacy of Examples 5 and 10 of Table II of Banholzer I and Banholzer II with identical dosing levels is maintained at 100% even after 20 hours. These results were determined under the responsibility and control of Dr. Reichl and submitted under cover of a Declaration under 37 C.F.R. § 1.132 in the matter of corresponding U.S. patent application Serial No. 09/976,950 (hereinafter the Reichl Declaration). The graphic illustration of these results is depicted in ANNEX 3.

9. I hereby declare that the experimental results obtained for the tested compounds according to the Meissner *et al.* application indicate that these compounds may fit into the pharmacological profile necessary for a once-a-day drug, whereas the Banholzer I and Banholzer II compounds show such an extremely long duration of action that they are not useful for a once-a-day mode of administration. Furthermore, I conclude that this superiority of the Meissner *et al.* compounds was neither taught, suggested, nor deducible by the cited prior art. Moreover, I conclude that these findings would have been both surprising and unexpected to one of ordinary skill in the art at the time the invention was made.

The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and

further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: July 18th, 2003 Signature:

(Michael Paul Pieper)

ANNEX 1

Method for the Determination of Bronchoprotection Against Acetylcholine-Induced Bronchospastic Collapse in Guinea Pigs After Inhalative Administration of Aqueous Solutions Containing the Tested Compounds (According to the Kallos-Pagel Model)

Animals

Male guinea pigs (breed: Dunkin-Hartley, Pirbright White) were purchased from Harlan Winkelmann/Borchen, Germany. The guinea pigs were housed in single Macrolon type III cages with softwood granulate bedding (Lignocel, type ¾) purchased from Rettenmayer & Söhne, Holzmühle, Germany. The guinea pigs had free access to pelleted food (Type Ssniff/MS-Zucht 4 mm Pellets, Altromin, Lage, Germany) and drinking water in a special air conditioned animal room (temperature 23°C, humidity 44% to 45%) with a light dark cycle of 12 hours.

Spasmogen

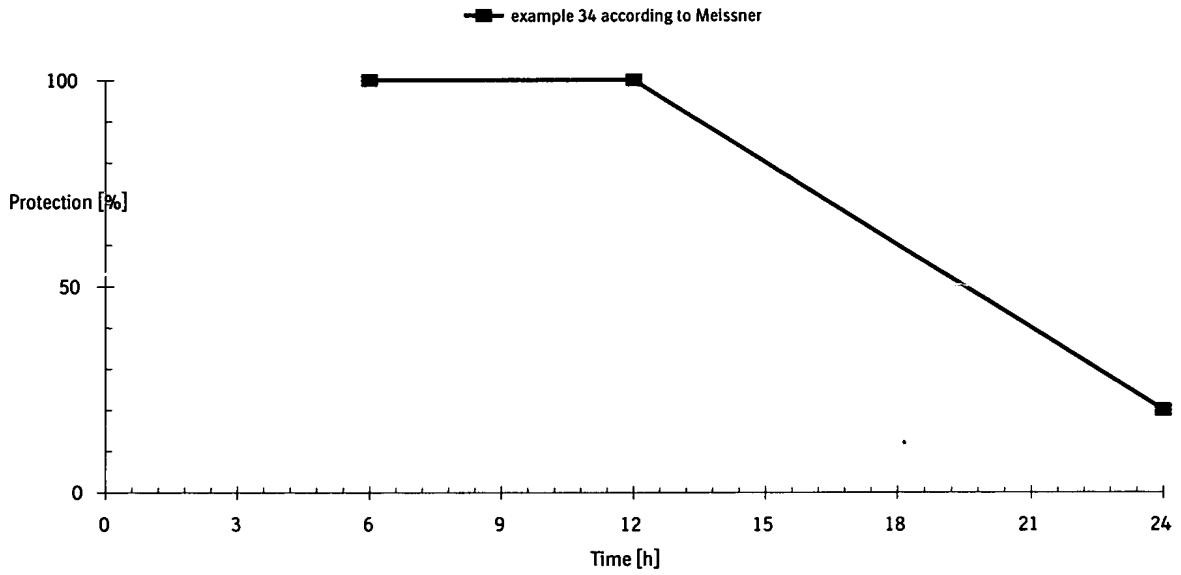
Acetylcholine chloride (ACh) was purchased from Sigma Diagnostics, St. Louis, MO, USA

Acetylcholine-Induced Bronchoconstriction

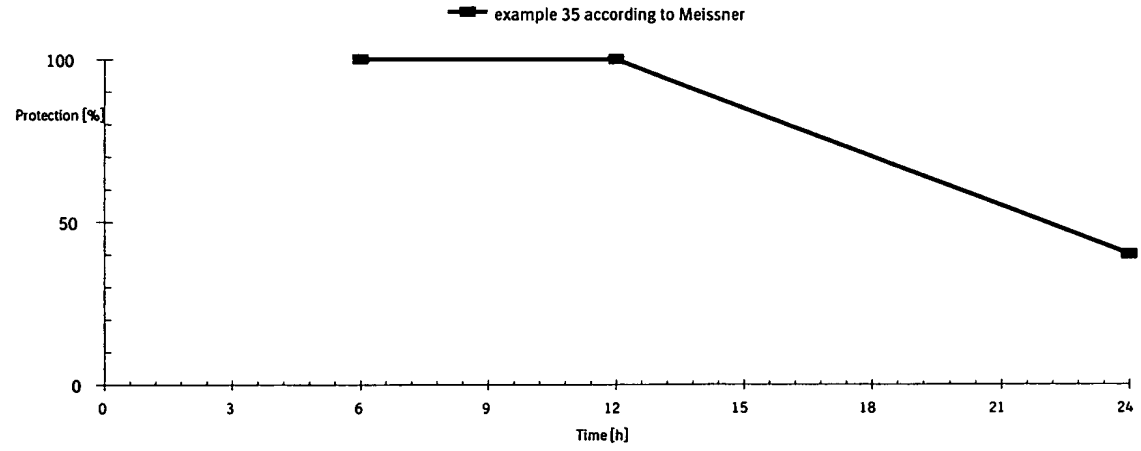
The experiments were performed using a modified method of that described by Kallos and Pagel (1937). In detail, guinea pigs were placed individually into a Plexiglas inhalation box filled with an aerosol, prepared from an 1% aqueous acetylcholine chloride solution, using a nebulizer (Inhalette, Dräger, Lübeck, Germany) with compressed air (200 kPa). The animals developed dyspnea and collapsed. Thereafter the animals were removed immediately. The time until the animals collapsed due to bronchoconstriction was recorded. The inhalation of aqueous solutions of the test compounds (3 mg/mL) was performed in the same way as described for ACh. The exposure time to anticholinergic compounds was 60 seconds. Animals were challenged with ACh aerosol at different time points after inhalation of the respective test compound. Animals which passed the threefold time interval of the corresponding control groups were recorded as protected. The percentage of protected animals was calculated.

ANNEX 2

Graphic illustration of the results obtained according to the Kallos-Pagel Model for the compounds according to the Meissner *et al.* application



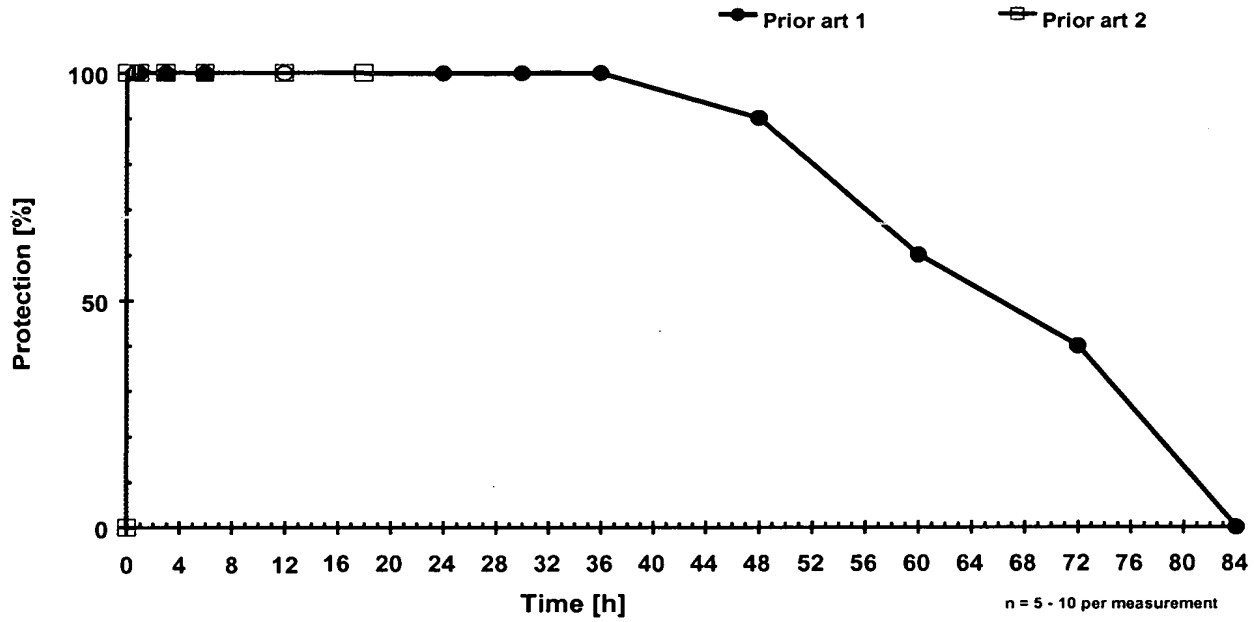
The foregoing results were obtained for example 34 according to the Meissner et al. application at a concentration of 3 mg/mL.



The foregoing results were obtained for example 35 according to the Meissner *et al.* application at a concentration of 3 mg/mL.

ANNEX 3

Graphic illustration of the results obtained according to the Kallos-Pagel Model for the Banholzer I and Banholzer II compounds



Legend:

prior art 1 is Example 10 of Table II of Banholzer I and Banholzer II as determined according to the Reichl Declaration; and

prior art 2 is Example 5 of Table II of Banholzer I and Banholzer II as determined according to the Reichl Declaration.

Dosing: all compounds were administered at a concentration of 3 mg/mL.